UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,261	12/02/2003	Hua Wang	22727/04148	5627

24024 7590 05/11/2007

CALFEE HALTER & GRISWOLD, LLP
800 SUPERIOR AVENUE
SUITE 1400
CLEVELAND, OH 44114

EXAMINER	
CHO, DAN SUNG C	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
05/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,261	WANG ET AL.	
	Examiner	Art Unit	
	Dan-Sung C. Cho	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *5-20 and 25-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/21/2004, 8/24/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignments (3 pages)*.

DETAILED ACTION

1. This action is in response to the papers filed 4/12/2007. Currently, claims 1-30 are pending. Claims 5-20 and 25-30 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I, Claims 1-4 and 21-24 and SEQ ID NOs: 1, 2, 4 in the paper filed on 4/12/2007 is acknowledged. Claims 5-20 and 25-30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The requirement is made FINAL.

Priority

3. This application claims benefit of 60/513,246 filed on 10/22/2003 and claims benefits of 60/500,736 filed on 09/05/2003 and 60/430,202 filed on 12/02/2002.

Specification Objections

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See, for example, page 14, line 4. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

5. Claims 1 and 21 are objected to because of the following informalities: Claim 1 contains typographical error: "sequence, :" in line 12 (the comma usage). The step iii in

line 13 is labeled as "(ii)". Claim 21, line 2 recites " i.)" and indented differently than steps ii) to iv). Appropriate correction is required.

6. Claims 2-4 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 2-4 fail to further limit claim 1 because the elected primer and probe sequences of SEQ ID NOs: 1, 2, and 4 hybridizes to positions 214-232 (SEQ ID NO: 1); to positions 260-276 (SEQ ID NO: 2); and to positions 354-369 (SEQ IN NO: 4) (see included "Sequence alignments", page 1, section 2). Claim 1 the instant claims depend from, recite the limitations of "within the sequence of nucleotide position of 1327 through nucleotide position 1460 of SEQ ID NO: 78" in lines 6-7, 10-11, and 15-16. Therefore, claims 2-4 do not further limit "within the sequence of nucleotide position of 1327 through nucleotide position 1460 of SEQ ID NO: 78".

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4, 21-24 are indefinite Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear whether the claim is drawn to a method for detecting Alicyclobacillus and Geobacillus or a method of determining the presence

of contamination by Alicyclobacillus or Geobacillus. The preamble states that the method is for method for detecting Alicyclobacillus and Geobacillus but the final process step is a method of determining the presence of PCR products wherein the presence of a PCR product in the sample is indicative of contamination by "Alicyclobacillus or Geobacillus or both". Therefore the claims are unclear as to whether the method is a method for detecting Alicyclobacillus and Geobacillus or a method of determining contamination by Alicyclobacillus or Geobacillus.

Claims 2-4 are indefinite over the recitation of the elected sequences of SEQ ID NOs: 1, 2, and 4. SEQ ID NO: 1 is identical to SEQ ID NO: 78, positions 214-232; SEQ ID NO: 2, to positions 260-276; and SEQ IN NO: 4, to reverse complementary sequence of 354-369 (see included "Sequence alignments", page 1, section 2). However, claim 1 the instant claims depend from, recite the limitations of "within the sequence of nucleotide position of 1327 through nucleotide position 1460 of SEQ ID NO: 78" in lines 6-7, 10-11, and 15-16. Therefore, claims 2-4 do not further limit "within the sequence of nucleotide position of 1327 through nucleotide position 1460 of SEQ ID NO: 78" limitations in claim 1, the instant claims depend from. It is unclear whether the primers and probe in the instant claim hybridizes to sequences within positions 1327 to 1460 or 214 to 369.

Claim 21 is indefinite over the recitation of the terms "under stringent conditions" in line 4 because the metes and bounds of the invention are not clear. "Stringent conditions" encompass low, medium or high stringencies. The claims are indefinite with regard to the conditions encompassed. The specification discloses PCR primer

selection parameters in page 13, para 4, but does not specify what "stringent conditions" are.

Claim 24 is indefinite over the recitation of the terms "acidic bacteria" in line 1 because the metes and bounds of the invention are not clear. The claims are indefinite with regard to what would make a bacterium acidic. The specification teaches acidophilic bacteria such as B. acidocaldarius, B. acidoterrestris, and B. cycloheptanicus in page 2, lines 1 and 2, but not acidic bacteria. The art teaches that acidophilic bacteria are found in acidic environments. It is not clear therefore if "acidic bacteria" are acidophilic bacteria or to some other bacteria.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 21-22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hristova (Hristova et al., 2001, Applied and Environ. Microbiol. 67: 5154-5160) in view of Yamazaki (Yamazaki et al., 1996, Letters in Applied Microbiol. 23: 350-354) and GenBank (GenBank Accession Numbers: AB042058, 2/2002), and further in view of Hogan (Hogan et al; US Pat. 5,541,308, July 30, 1996), Newton (PCR Essential Data, edited by C.R. Newton, 1995, Chapter 6, Primers, pages 49-56) and Buck (Buck et al., 1999, Biotechniques 27(3): 528-536).

Claim 1 is indefinite because the preamble recites detection of "Alicyclobacillus and Geobacillus" but the final step in the claim is to determining contamination with Alicyclobacillus or Geobacillus or both as explained above. Therefore, the instant claim is interpreted as detection of Alicyclobacillus.

With regard to claim 1, step (a), Hristova teaches a method of amplifying a target DNA by real-time TaqMan PCR. With regard to claim 1, (a), (i), Hristova teaches a method wherein the forward primer, 963F, is used to amplify and detect PM1 16S rDNA (Table 2, Figure 2). The 963F forward primer is 28 nucleotides in length and has 100% sequence identity, therefore capable of hybridizing, to the consecutive sequences from position 963 to 990 of PM1 16S rDNA (See Sequence alignments included, section 1). With regard to claim 1, (a), (ii), Hristova teaches a method wherein the reverse primer, 1076R, is used (Table 2). The primer is 22 nucleotides in length and has 100%

sequence identity, therefore capable of hybridizing, to the consecutive sequences from position 1056 to 1076 of PM1 16S rDNA and wherein the position of the reverse primer is 3' or downstream of the forward primer site (See Sequence alignments included, section 1). With regard to claim 1, (a), lines 13-17, Hristova teaches a method wherein the probe, 1030T, is used (Table 2), wherein the primer is 21 nucleotides in length and has 100% sequence identity, therefore capable of hybridizing, to the consecutive sequences from position 990 to 1011 of PM1 16S rDNA (See Sequence alignments included, section 1), which hybridizes to the sequences between the two primer sites.

With regard to claim 1, (b), Hristova teaches a method wherein the primer set is used in PCR (page 5156, left col., para 4, lines 1-4). With regard to claim 1, (c), Hristova teaches a method wherein the presence of PCR products is indicative of contamination of the test sample by PM1 bacteria (page 5156, right col., para 3 and Figure 2). Hristova teaches a method wherein the probe is labeled with a marker, FAM, which emits a signal upon hybridization of the probe to the target nucleic acid sequence (page 5156, left col., para 2, line 6); and detecting the emitted signal of the sample (page 5156, left col., para 5, line 10-12). Hristova teaches a method wherein the emitted signal of the sample is detected (page 5156, left col., para 5, lines 10-14).

With regard to claim 22, Hristova teaches that the PCR amplification is quantitative PCR (Figures 1 and 2).

With regard to claim 23, Hristova teaches that the PCR amplification method is real-time PCR (page 5156, right col., para 3, line 2).

Hristova does not teach a method wherein Alicyclobacillus is detected by

detecting its 16S rDNA positions 1327-1460 of SEQ ID NO: 78.

However the complete 16S sequences of several Alicyclobacillus species are known (GenBank Accession Number: AB042058, 2/2002, a copy included). Additionally, Yamazaki teaches a method of detecting Alicyclobacillus acidoterrestris stains by PCR amplification in apple juice (page 351, left col para 2, line 1; page 352, left col, para 5, lines 1-7). Yamazaki teaches that detection of thermophilic acidophilic spore-forming bacteria is essential to the quality control of various beverages (page 350, left col., para 3, lines 1-2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to adapt the TaqMan PCR method of Hristova for detection of Alicyclobacillus as taught by Yamazaki in view of the available sequences of the Alicyclobacillus 16S sequences taught by GenBank. The ordinary artisan would be motivated to adapt the TaqMan PCR methods of Hristova to detect Alicyclobacillus whose 16S sequence are taught by GenBank, because Yamazaki teaches that detection of thermophilic acidophilic spore-forming bacteria is essential to the quality control of various beverages.

In addition, Hogan teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of oligonucleotides,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (column 10, lines 13-15). Hogan teaches that probes may be labeled using a variety of labels, as described within, and may be incorporated into diagnostic kits.

Newton teaches how to design primers. With regard to claim 21, (i), Newton teaches that primers should not have unusual sequences such as repetitive motives (page 51, left col, para 1, lines 7-9). Therefore Newton teaches a primer design wherein stretches of same nucleotide bases should be avoided. Newton teaches that primers should not have complementarity of 3' ends either inter or intra individual (page 51, left col, para 1, lines 7-9). Therefore it would have been prima facie obvious to the ordinary artisan to avoid palindromic sequences in a primer that form intra hybrids due to complementarity, based on the teachings of Newton. Newton teaches primers should not have sequences that hybridize to other portions of the same primer forming an

"intra" hybridized molecules due to complementarity. Newton teaches that primers should not hybridize to one another or form "primer-dimer" (page 51, left col, para 1, lines 12-13). Newton teaches that primers should have 40-60% GC content (page 51, left col, para 1, last line). Newton teaches that a good primer design maximize both the specificity and efficiency of the amplification reactions and avoid misdiagnosis (page 49, left col., para 1, lines 1-2).

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers

in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made adapt the TaqMan method of Hristova to detect Alicyclobacillus by designing and making additional Alicyclobacillus 16S primers and probes as taught by Yamazaki in view of the sequences taught by GenBank and the guidance taught by Hogan, Newton and Buck, including the primers and probes that would hybridize to region 1327-1460, wherein primers and probes with no "runs of more than 5 of the same nucleotide bases" and palindromic sequences, sequences that would lead to "primer-dimer"; and primers with 40-60% GC content would be selected.

Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Yamazaki, Hristova, Hogan, Newton and Buck. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested new primers and probes to obtain additional oligonucleotide primers and probes that function to detect Alicyclobacillus 16S and identify oligonucleotides with improved properties, including primers and probes that would hybridize to region 1327-1460.

10. Claims 2-4 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hristova, Yamazaki, GenBank, Hogan, Newton and Buck as applied to claims 1, 22-23 above, and further in view of in view of Goto (Goto et al., J of Gen. Appl. Microbiol. 2000, 46: 1-8).

The teachings of Hristova, Yamazaki and GenBank, Hogan, Newton and Buck as applied to claims 1, 22-23, are as set forth above.

Hristova, Yamazaki, GenBank, Hogan, Newton and Buck do not teach detection of Alicyclobacillus with the specific sequences of primers and probes in SEQ ID NOs: 1, 2 and 4 and by detecting the 5' region of 16S rDNA sequences SEQ ID NOs 1,2 and 4 hybridize.

However, Goto teaches a method of detecting Bacillus species (page 2, right col. para 2, lines 16-18). Goto also teaches detection of PCR amplified 16S HV regions of other related genera, a Alicyclobacillus (page 7, para 2, line 2). Goto teaches that the methods were used to specifically amplify fragments with the 5' end region of their 16S rDNA that corresponds to the HV region of genus Bacillus (page 7, para 2, lines 7-13). Therefore, Goto teaches a method of detecting the Alicyclobacillus by PCR amplification methods wherein the same 5' end region of the 16S rDNA is detected. SEQ ID NO: 1 of the instant application hybridizes to positions 214-232; SEQ ID NO: 2 hybridizes to positions 260-276; and SEQ ID NO: 4, to positions 354-269 of a Alicyclobacillus 16 rDNA sequence (AB042058) GenBank teaches (See sequence alignment).

Therefore, it would have been prima facie obvious to one of ordinary skill in the

art at the time the invention was made adapt the TaqMan methods of Hristova, Yamazaki, GenBank, Hogan, Newton and Buck to detect Alicyclobacillus by designing and making additional probes and primers that can detect Alicyclobacillus by directing probes and primers to the 5' HV region as taught Goto, including the primers and probes comprising SEQ ID NOs: 1, 2, and 4.

The ordinary artisan would be motivated to have designed and tested new primers and probes to obtain additional oligonucleotide primers and probes that function to detect Alicyclobacillus 5' HV region of the 16S rDNA because Goto teaches that the method of amplifying and detecting multiple strains together is useful for the identification of large number of species for an efficient indexing and rapid identification of groupings of Bacillus-related species such as Alicyclobacillus, which used to be classified with Bacillus as explained above.

Conclusion

11. **No claims are allowed.**

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Dan-Sung C. Cho whose telephone number is (571) 272-9933. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

4/30/07

Dan-Sung C. Cho
Examiner
AU1634

Jehanne Sitton

JEHANNE SITTON
PRIMARY EXAMINER

4/30/07